Alcohol Consumption Mediates the Relationship Between *ADH1B* and DSM-IV Alcohol Use Disorder and Criteria

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ABSTRACT. Objective: A single nucleotide variation in the alcohol dehydrogenase 1B (*ADH1B*) gene, rs1229984, produces an ADH1B enzyme with faster acetaldehyde production. This protective variant is associated with lower alcohol consumption and lower risk for alcohol use disorders (AUDs). Based on the premise that faster ADH1B kinetics decreases alcohol consumption, we formally tested if the association between *ADH1B* variant rs1229984 and AUDs occurs through consumption. We also tested whether the association between rs1229984 and each of the 11 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), AUD criteria occurs through consumption. **Method:** A total of 1,130 lifetime drinkers from an Israeli household sample were assessed with a structured interview and genotyped for rs1229984 (protective allele frequency = 0.28). Logistic regression evaluated the association between rs1229984 and each phenotype (AUDs, 11 individual DSM-IV criteria). For phenotypes significantly related to rs1229984, the effect through consumption was tested with logistic regression and bootstrapping. **Results:** *ADH1B* rs1229984 was significantly associated with AUDs and six criteria, with odds ratios ranging from 1.32 to 1.96. The effect through consumption was significant for these relationships, explaining 23%–74% of the total *ADH1B* effect. **Conclusions:** This is the first study to show that *ADH1B* rs1229984 is related to 6 of the 11 DSM-IV AUD criteria and that alcohol consumption explained a significant proportion of these associations and the association of *ADH1B* with AUDs. Better understanding of the relationship between *ADH1B* and the DSM-IV AUD criteria, including effects through consumption, will enhance our understanding of the etiologic model through which AUDs can occur. (*J. Stud. Alcohol Drugs, 75,* 635–642, 2014)

ALCOHOL USE DISORDERS (AUDs; alcohol dependence or abuse) are an important public health issue because of their substantial impact on physical and mental health (Rehm et al., 2009). Although many factors influence the risk of AUDs, the contribution of genetic factors is important. Alcohol dehydrogenase genes are among the most widely studied risk genes for AUDs (Rietschel and Treutlein, 2013) because they determine the forms of the enzymes that convert alcohol (ethanol) to acetaldehyde during alcohol metabolism (Bosron et al., 1993; Thomasson et al., 1993).

A single nucleotide polymorphism (SNP) in the alcohol dehydrogenase gene *ADH1B* (rs1229984) is significantly associated with the risk for AUDs. This finding is particularly robust in East Asian populations in which the minor allele frequency is high (Li et al., 2011; Thomasson et al., 1991), but also significant in European populations with lower to intermediate minor allele frequencies (Bierut et al., 2012; Meyers et al., 2013). Lower risk for AUD is found among individuals with the minor allele that encodes the more active form of the enzyme. This form, producing faster conversion of ethanol to acetaldehyde (Edenberg, 2007; Hurley and Edenberg, 2012; Thomasson et al., 1993), is assumed to produce aversive effects, leading to lower alcohol consumption. However, no study has formally examined the role of alcohol consumption in this set of relationships. Because *ADH1B* has previously been demonstrated to be related to alcohol consumption (Bierut et al., 2012; Hasin et al., 2002a; Meyers et al., 2013; Spivak et al., 2007), and there is considerable overlap between the genetic influences on alcohol consumption and AUDs (Grant et al., 2009; Kendler et al., 2010), here we formally test whether and to what extent the *ADH1B* relationship to AUDs is explained by its effect on alcohol consumption.

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An additional consideration is that AUDs are diagnosed according to a set of 11 dependence or abuse criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994). To better understand the effects of *ADH1B* on AUDs, the relationship of *ADH1B* to each individual criterion should be determined. Although previous studies examined the association between rs1229984 and AUDs in an Israeli sample (Meyers et al., 2013), the present study aims to increase our understanding of *ADH1B* effects in this sample by determining which of the AUD criteria underlie the association of rs1229984 with AUDs and whether an indicator of maximum alcohol consumption mediates these relationships. A previous study assessing the relationship between *ADH1B* SNPs and alcohol dependence phenotypes such as "severe use" and "withdrawal" (Gizer et al., 2011) found significant evidence of an association with withdrawal symptoms. However, to our knowledge, no study has evaluated the relationship between *ADH1B* and each of the DSM-IV alcohol dependence or abuse criteria separately and whether these relationships are explained by the *ADH1B* effect on consumption.

To address these issues, we first examined the effect of *ADH1B* rs1229984 on the risk for lifetime AUDs through its effects on consumption. Second, we evaluated the effects of *ADH1B* on each of the DSM-IV lifetime AUD criteria. Third, for those criteria significantly associated with *ADH1B,* we assessed whether *ADH1B* acted on these criteria through alcohol consumption. This study used data from a large general population sample of Israeli Jews (Shmulewitz et al., 2010, 2012), where we previously showed a strong association between *ADH1B* and other alcohol phenotypes including alcohol dependence, AUDs, and AUD severity (Meyers et al., 2013).

Method

Study procedures

Data were collected in 2007–2009 from 1,349 Jewish adult household residents, as described in detail previously (Hasin et al., 2002a, 2002b; Shmulewitz et al., 2010, 2012). The sample was designed to investigate environmental and genetic influences on alcohol-related traits. Adult residents of Jewish ethnicity were selected from the Israeli Population Register by the Israeli Bureau of the Census. The Israeli Population Register comprises household residents in all areas of Israel; potential respondents were selected from the registry based on their demographic characteristics and to provide diversity in their area of residence. Men were oversampled, as drinking among Israeli women is limited (Shmulewitz et al., 2010). Participants of Jewish ethnicity were selected to provide sample homogeneity for the genetic research questions.

Interviewers received structured training and administered face-to-face computer-assisted interviews after obtaining written informed consent, as approved by relevant American and Israeli institutional review boards (Shmulewitz et al., 2010). Interviews were administered in Hebrew or Russian. As described previously (Hasin et al., 2002a, 2002b; Shmulewitz et al., 2012; Spivak et al., 2007), translation of the interview followed standard translation–back translation procedures in use by the World Health Organization, with extensive collaboration between Americans and Israelis fluent in Hebrew, Russian, and English. The overall response rate was 68.9%. Quality control included field observation, reviews of recorded interviews, and telephone verification of responses.

Sample

The present analysis is based on 1,130 ever-drinkers (respondents who reported at least one sip of alcohol, lifetime) after excluding respondents who (a) did not provide information on drinking ($n = 2$), (b) were never exposed to alcohol ($n = 67$), or (c) were ever-drinkers but were missing genotypes for the *ADH1B* SNP rs1229984 ($n = 150$). Based on previous work in this sample (Hasin et al., 2002a, 2002b; Shmulewitz et al., 2012; Spivak et al., 2007), demographic covariates associated with alcohol-related phenotypes were age, sex, and emigration from the former Soviet Union (FSU). Of those participating, 25.1% ($n = 284$) were 21–29 years old, 33.6% ($n = 380$) were 30–44, and 41.2% ($n = 466$) were 45 or older; 78.3% ($n = 885$) were male; and 23.9% ($n = 270$) were emigrants from the FSU.

Measures

DSM-IV alcohol use disorder and criteria. The Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS; Grant et al., 1995, 2003) was used to assess the alcohol abuse and dependence criteria following DSM-IV guidelines (American Psychiatric Association, 1994). Binary variables were created for each of the seven alcohol dependence criteria (tolerance: diminished effect with same quantity or need more to get desired effect; larger/longer: drinking more or for longer periods than intended; quit/control: inability to quit despite attempts or desire to stop/drink less; time spent: excessive time spent obtaining, using, or recovering from alcohol; activities given up: giving up important activities to drink; withdrawal: evidence of the withdrawal syndrome or alcohol/other related substances taken to prevent/relieve symptoms; and physical/psychological: continued drinking despite physical and/or psychological problems associated with use). Binary variables were similarly created for the four alcohol abuse criteria (hazardous use: drinking in situations where it is physically hazardous to do so; social problems: drinking despite issues with social contacts resulting from alcohol use; neglect roles: drinking causing interferences with work, home, or school responsibilities; and legal problems: arrest or other legal problems associated with drinking).

A binary variable was created for AUDs by combining diagnoses for lifetime alcohol dependence (three or more dependence criteria within a 12-month period) and alcohol abuse (one or more abuse criteria in the absence of lifetime alcohol dependence). Reliability and validity of AUDADIS-IV alcohol diagnoses in clinical and general population samples, in U.S. and international studies, ranges from good to excellent (Chatterji et al., 1997; Grant et al., 1995, 2003; Hasin et al., 1997). Reliability of DSM-IV criteria was similarly found to be good (majority of κ values exceed .60; Chatterji et al., 1997). The lifetime timeframe was used throughout (except for one sensitivity analysis) because genetic effects could be missed if only the current timeframe was used.

Alcohol consumption—Maxdrinks. Using the AUDADIS alcohol consumption measures, we created a variable indicating maximum number of drinks in a 24-hour period during period of heaviest drinking (Maxdrinks; Meyers et al., 2013; Shmulewitz et al., 2012), similar to the maximum drinks variable used previously in genetic studies (Dawson et al., 2010; Greenfield et al., 2006; Malone et al., 2002; Saccone et al., 2000; Schuckit et al., 2002; Schumann et al., 2003; Shea et al., 2001; Spivak et al., 2007; Yang et al., 2005). AUDADIS consumption items have good psychometric properties and good to excellent interrater reliability (intraclass correlation coefficients for all consumption items = .59–.99; .70 for Maxdrinks specifically) and excellent validity (Grant et al., 1995, 2003; Hasin et al., 1997). Because the distribution of Maxdrinks was skewed (Meyers et al., 2013), for the mediation analysis, Maxdrinks was transformed to have a mean of 0 and standard deviation of 1.

Genotyping. Genotyping procedures have been detailed elsewhere (Meyers et al., 2013). In brief, DNA was extracted from blood or saliva samples using standard techniques. The Sequenom MassArray (Sequenom, San Diego, CA) was used to genotype *ADH1B* SNP rs1229984; no evidence of deviation from Hardy–Weinberg equilibrium was found. Both genotype groups with the protective allele A (AA and AG) showed similar prevalences for DSM-IV alcohol criteria; therefore, they were combined into one group. Higher criteria prevalences were found in those without allele A (genotype group GG). Thus, we define "high risk" as the absence of allele A, leading to a group that constitutes 52.6% of our sample. We compare the genetically high-risk group to the low-risk group (genotypes AA or AG) in our analyses. Ancestry-informative markers were included to assess population stratification (Listman et al., 2010). Genotypes at rs1229984 were not associated with age, sex, or FSU status.

Statistical analysis. Chi-square analysis evaluated differences in criterion prevalence by demographic subgroup.

Regression analysis. Logistic regression (SAS Version 9.2, SAS Institute Inc., Cary, NC) assessed association of the rs1229984 high-risk group with each phenotype (AUDs and each alcohol abuse or dependence criterion). Analyses were adjusted for sex, age, and FSU status, because drinking behavior differs by these subgroups in Israel (Hasin et al., 2002b; Shmulewitz et al., 2012; Spivak et al., 2007). Results are reported as odds ratios (OR), the exponential of the regression coefficient τ, indicating the increase in the odds of the phenotype in the high-risk group. For each phenotype significantly associated with *ADH1B,* two additional regressions were performed to evaluate the effect through Maxdrinks (Baron and Kenny, 1986): (a) Maxdrinks was regressed on *ADH1B* (regression coefficient = α); (b) each phenotype was regressed on *ADH1B* with Maxdrinks in the model (regression coefficient for Maxdrinks = β; for *ADH1B* = τ'; Figure 1). The effect of *ADH1B* through Maxdrinks was calculated as $\alpha\beta$ ("product of the coefficients" (Sobel, 1982; Figure 1), with a significant effect indicated by $\alpha\beta$ significantly greater than 0. To determine the significance of $\alpha\beta$, we created 1,000 bootstrapped samples to generate empirical percentile confidence intervals (CIs) and *p* values since the distribution of $\alpha\beta$ for nonnormal outcomes is unknown (Bollen and Stine, 1990; Shrout and Bolger, 2002). Empirical 95% CIs were computed by ordering the $\alpha\beta$ values from the bootstrapped samples from lowest to highest; the 25th value represents the lower bound (2.5%), and the 975th value represents the upper bound (97.5%). *P* values were the percentage of bootstrapped samples with $\alpha\beta$ of 0 or less.

The percentage of the *ADH1B* effect explained by Maxdrinks was calculated as follows: $\{[\exp(\tau) - \exp(\tau')] / [\exp(\tau) - 1]\} \times 100$, where $\exp(\tau)$ is the OR for the *ADH1B* effect without Maxdrinks in the model (Model A), and $\exp(\tau')$ is the OR with Maxdrinks in the model (Model B) (Shmulewitz et al., 2012). When there is no effect—that is, the OR for the *ADH1B* effect is the same in both regression models [$\exp(\tau) = \exp(\tau')$]—this equation evaluates to 0%. When there is no remaining *ADH1B* effect with Maxdrinks included in the model [$\exp(\tau') = 1$], this equation evaluates

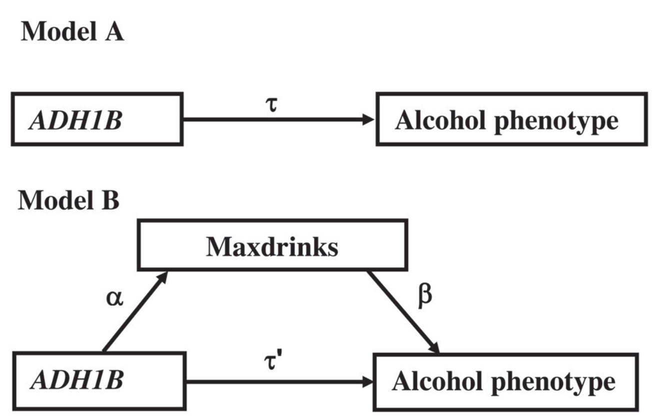

FIGURE 1. Path diagram for Model A, the total effect (τ) of *ADH1B* on drinking phenotypes, and model B, the direct (τ') and indirect (through the Maxdrinks; $\alpha\beta$) effect of *ADH1B* on drinking phenotypes. Note: *Alcohol phenotype* refers to each criterion or any alcohol use disorder.

TABLE 1. Prevalence of DSM-IV alcohol abuse/dependence criteria and relationship to demographic variables

Criterion	Overall prevalence, %	Sex: % men	Sex: % women	Sex: χ^2	Age, in years: % 20–29	Age: % 30–44	Age: % ≥45	Age: χ^2	FSU status: % FSU	FSU status: % non-FSU	FSU status: χ^2
Alcohol dependence											
Tolerance	33.2	37.0	19.6	26.07****	55.0	33.4	19.7	95.55****	33.0	33.3	0.01
Quit/control	12.5	14.2	6.1	11.57*	18.0	12.9	8.8	13.65*	13.7	12.1	0.49
Larger/longer	34.2	38.0	20.4	26.30****	50.0	35.8	23.2	57.13****	40.4	32.2	6.09*
Time spent	10.4	11.9	4.9	10.03*	16.9	9.2	7.3	18.85*	9.6	10.6	0.20
Activities given up	2.0	2.4	0.4	3.88*	1.8	2.6	1.5	1.47	4.1	1.3	8.41*
Withdrawal	14.7	16.6	7.8	12.01*	23.6	15.8	8.4	33.18****	17.0	14.0	1.56
Physical/psychological	10.9	13.0	3.3	18.72****	15.5	12.1	7.1	13.75*	20.0	8.0	30.39****
Alcohol abuse											
Neglect roles	2.6	3.1	0.8	3.83	4.2	2.6	1.5	5.24	4.1	2.1	3.23
Hazardous use	16.8	20.2	4.5	33.97****	23.9	18.7	10.9	22.75****	25.2	14.2	17.77****
Social problems	8.6	10.6	1.2	21.59****	16.9	6.3	5.4	33.68****	17.4	5.8	35.20****
Legal problems	1.9	2.3	0.4	3.61	2.8	2.2	0.8	4.02	5.9	0.6	32.18****

Notes: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* FSU = emigrant from the former Soviet Union.
*$p < .05$; ****$p \leq .0001$.

to 100%. Empirical CIs and *p* values were calculated for this percentage.

Exploratory analysis. To further explore the association of *ADH1B* with AUDs and the individual AUD criteria, a latent variable model was examined using Mplus Version 6.12. In this model, the association between *ADH1B* and an AUD latent variable, indexed by the 11 criteria, was examined, in addition to simultaneous logistic regressions of each individual criterion and *ADH1B.* Control variables (age, sex, FSU status) were also included in this model.

Results

The overall prevalence of the abuse or dependence criteria ranged from 1.9% to 34.2% (Table 1). The most commonly endorsed dependence criterion was drinking more or over longer periods than intended (larger/longer; 34.2%), and the most commonly endorsed abuse criterion was drinking in situations where it is physically hazardous to do so (hazardous use; 16.8%). Men were significantly more likely to endorse all criteria except neglect of major roles and legal problems (Table 1). Younger individuals were significantly more likely to endorse hazardous use, drinking despite social problems, and all dependence criteria except activities given up (Table 1). FSU emigrants were more likely to endorse larger/longer, activities given up, continued drinking despite physical and/or psychological problems associated with use (physical/psychological), and all abuse criteria except neglect roles (Table 1).

ADH1B, *alcohol use disorders, and individual criteria*

A higher prevalence of AUDs, as well as dependence and abuse criteria, was observed among the high-risk genotype group (Table 2). Prevalence values ranged from 2.4% to 39.6% and from 2.2% to 19.7% for dependence and abuse criteria, respectively (Table 2). After adjusting for demographic variables, *ADH1B*-rs1229984 was significantly associated with AUDs (OR = 1.77), as previously demonstrated for this population (Meyers et al., 2013). It was also significantly associated with 6 of the 11 criteria (Model A in Table 3): Individuals in the high-risk group had higher odds of endorsing tolerance (OR = 1.32), quit/control (OR = 1.45), larger/longer (OR = 1.75), physical/psychological (OR = 1.96), hazardous use (OR = 1.59), and social problems (OR = 1.63).

Effects mediated through Maxdrinks

In Model B (with Maxdrinks; Figure 1), the direct effect of *ADH1B* (τ') on AUDs and each associated criterion was less than in Model A (τ; Table 3), suggesting an effect that is at least partially mediated through Maxdrinks. The effect through Maxdrinks is depicted in regression Model B, where *ADH1B* significantly predicted higher Maxdrinks (α = .23), and Maxdrinks significantly predicted AUDs and each of the six associated criteria (β; Table 3). Thus, for each phenotype, $\alpha\beta$ was significantly greater than 0, indicating that part of the *ADH1B* effect is through its effects on Maxdrinks (Table 3). The percentage of the *ADH1B* effect explained by Maxdrinks was sizeable for AUDs (43.7%), larger/longer (34.6%), and physical/psychological (22.9%), but significant association remained with *ADH1B* even with Maxdrinks in the model. In contrast, for the other four criteria (tolerance [74.4% of the *ADH1B* effect due to Maxdrinks], quit/control [39.2%], hazardous use [46.6%], and social problems [45.1%]), the relationship with *ADH1B* was no longer significant with Maxdrinks in the model.

Exploratory analysis

In the exploratory analysis modeling AUD as a latent variable and regressing the AUD variable and the indi-

Table 2. Relationship between any alcohol use disorder (AUD)/alcohol criteria and *ADH1B*-rs1229984 among ever-drinkers (N = 1,130)

Phenotype	Prevalence[a] High-risk group (GG; n = 594)	Prevalence[a] Low-risk group (AA/AG; n = 536)	Wald $\chi^{2,b}$
Any AUD	29.6	20.2	13.46***
Alcohol dependence			
Tolerance	35.7	30.4	4.32*
Quit/control	14.3	10.5	3.96*
Larger/longer	39.6	28.2	17.54***
Time spent	11.6	9.0	2.24
Activities given up	2.4	1.5	1.04
Withdrawal	15.3	14.0	0.43
Physical/psychological	13.8	7.7	10.52**
Alcohol abuse			
Neglect roles	3.03	2.1	0.96
Hazardous use	19.7	13.6	7.49**
Social problems	10.4	6.5	4.49*
Legal problems	2.2	1.5	0.28

[a]From cross-tabulation; [b]from logistic regression adjusted for age, sex, emigrant from former Soviet Union status.
*p < .05; **p < .01; ***p < .001.

vidual criteria on *ADH1B, ADH1B* was not significantly associated with the AUD latent variable (regression coefficient = -.061, 95% CI [-.25, .12], p = .521), whereas the associations between *ADH1B* and the individual criteria were similar to those in the main analysis (presented above and in Table 3). For example, the same six criteria were significantly associated with *ADH1B:* tolerance (OR = 1.64, 95% CI [1.02, 2.64]), quit/control (OR = 1.64, 95% CI [1.01, 2.66]), larger/longer (OR = 2.72, 95% CI [1.59, 4.67]), physical/psychological (OR = 2.50, 95% CI [1.41, 4.45]), hazardous use (OR = 1.89, 95% CI [1.16, 3.08]), and social problems (OR = 2.23, 95% CI [1.05, 4.76]).

Discussion

In this study, we found that *ADH1B*-rs1229984 was related to AUDs and six individual DSM-IV AUD criteria in an Israeli household sample. A significant portion of the effect acts through Maxdrinks, supporting the premise that *ADH1B* effects on AUD criteria and diagnosis occur through limiting excessive alcohol consumption.

Table 3. Relationship between *ADH1B*-rs1229984 risk status and AUDs/alcohol criteria: without Maxdrinks (Model A) and with Maxdrinks (Model B) in the regression models

Criterion	Model A Maxdrinks not included: *ADH1B* effect on the alcohol phenotype (τ) OR[a] [95% CI]	Model B Maxdrinks included: Direct *ADH1B* effect on the alcohol phenotype (τ') OR[a] [95% CI]	Maxdrinks effect on the alcohol phenotype (β) OR[a] [95% CI]	Indirect effect of *ADH1B* on alcohol phenotype through Maxdrinks $\alpha\beta$ [95% CI][b]	% of *ADH1B* effect explained by Maxdrinks % [95% CI][b]
Any alcohol use disorder	1.77 [1.32, 2.37]****	1.45 [1.05, 2.00]*	2.94 [2.38, 3.64]****	0.25 [0.14, 0.40]***	43.7 [15.6, 80.8]***
Alcohol dependence					
Tolerance	1.32 [1.02, 1.73]*	1.08 [0.82, 1.44]	2.67 [2.16, 3.28]****	0.23 [0.12, 0.37]***	74.4 [23.2, 100.0]*
Quit/control	1.45 [1.01, 2.08]*	1.27 [0.87, 1.85]	1.60 [1.37, 1.86]****	0.11 [0.06, 0.17]***	39.2 [5.8, 100.0]*
Larger/longer	1.75 [1.35, 2.27]****	1.49 [1.13, 1.97]**	2.58 [2.10, 3.16]****	0.22 [0.12, 0.36]***	34.6 [15.3, 66.5]***
Time spent	1.35 [0.91, 2.00]	–	–	–	–
Activities given up	1.58 [0.65, 3.84]	–	–	–	–
Physical/psychological	1.96 [1.31, 2.95]**	1.74 [1.15, 2.65]**	1.55 [1.33, 1.81]****	0.10 [0.05, 0.16]***	22.9 [5.8, 58.0]**
Withdrawal	1.12 [0.80, 1.57]	–	–	–	–
Alcohol abuse					
Neglect roles	1.47 [0.68, 3.15]	–	–	–	–
Hazardous use	1.59 [1.14, 2.21]**	1.31 [0.92, 1.87]	2.20 [1.83, 2.65]****	0.18 [0.10, 0.30]***	46.6 [14.1, 100.0]**
Social problems	1.63 [1.04, 2.57]*	1.35 [0.83, 2.18]	1.89 [1.59, 2.26]****	0.15 [0.08, 0.24]***	45.1 [0.0, 100.0]*
Legal problems	1.28 [0.51, 3.18]	–	–	–	–

Notes: ADH1B effect on Maxdrinks α [95% CI]: 0.23 [0.13, 0.34], p < .0001. [a]OR = odds ratio, from logistic regression adjusted for sex, age, emigrant from former Soviet Union status: the exponential of the corresponding regression coefficients τ, τ', or β (Figure 1); [b]empirical percentile confidence interval from 1,000 bootstrapped samples.
*p < .05; **p < .01;***p < .001; ****$p \leq$ .0001.

Although previous studies found robust associations between *AHD1B* and AUDs in Asian (Li et al., 2011), European (Bierut et al., 2012), and Israeli samples (Hasin et al., 2002b; Meyers et al., 2013), this is the first study to examine the association between *ADH1B* and each DSM-IV criterion individually. Our main results suggest that the association between *ADH1B* and AUDs may be explained by the association of *ADH1B* with six criteria, further supported by the results of our exploratory latent variable model. Although the low prevalence of certain criteria (i.e., activities given up, neglect roles, legal problems) may have led to low power for detecting significant associations with these criteria, a recent twin study suggested that multiple genetic factors may be associated with the different dependence criteria (Kendler et al., 2012), supporting the possibility that other genetic factors influence the risk for the criteria that were unrelated to *ADH1B* in this sample. Studies in populations with substantially higher prevalence of these criteria (i.e., clinical samples, see Hasin et al., 2012) are needed to determine the relationship of these less frequent AUD criteria to *ADH1B.*

This is the first study to formally test the long-held assumption that the protective allele of *ADH1B*-rs1229984 influences AUD risk by limiting alcohol consumption. We did this by showing that a substantial proportion of the *ADH1B* effect acts through consumption (Maxdrinks). Similarly, much of the *ADH1B* effect on the six associated DSM-IV AUD criteria acts through Maxdrinks. The remaining effect of *ADH1B* on AUDs (after accounting for mediation through Maxdrinks) may be attributable to the unobserved *ADH1B* effect on other criteria (as discussed above) or the remaining *ADH1B* effect on larger/longer and physical/psychological. For these criteria, other mechanisms may account for the remaining *ADH1B* effect, such as interaction with environmental factors (i.e., stress; Keyes et al., 2012) or other *ADH* or neuronal genes, common to many externalizing disorders (i.e., *GABRA2;* Agrawal and Bierut, 2012).

The analysis presented here used the Maxdrinks variable to indicate alcohol consumption because subjective adverse effects of the alcohol metabolism process may limit the maximum quantity of alcohol a person can consume. Other alcohol consumption variables could also have been used. As a post hoc sensitivity analysis, we used a variable, "usual drinks" (defined as the number of drinks a respondent usually had/has in a single day, during period of heaviest drinking), in place of Maxdrinks. Similar to Maxdrinks, usual drinks was related to *ADH1B* (regression coefficient = .21; 95% CI = [.07, .34], p = .0026), but usual drinks showed a weaker relationship to the alcohol phenotypes (any AUD, each AUD criterion). Therefore, the mediation effect for usual drinks was lower than for Maxdrinks. These results suggest that the Maxdrinks consumption indicator better explains the relationship of *ADH1B* to alcohol phenotypes.

Study limitations are noted. First, although gene association studies are potentially confounded by population stratification, a previous study in this sample (Meyers et al., 2013) showed no confounding by population stratification of the relationship between *ADH1B* and AUDs or Maxdrinks. Nevertheless, significant associations of *ADH1B* with each alcohol criterion were re-analyzed adjusting for population substructure among participants with ancestry informative markers available (n = 1,096). Results were quite similar, although with slightly larger CIs and p values (most likely because of smaller sample size), indicating that the associations did not arise solely because of confounding by population substructure. Second, we may be detecting significant signals from variants that are in linkage disequilibrium with *ADH1B*-rs1229984. However, enzymatic studies show that this *ADH1B* variant is functional, affecting enzyme kinetics (Bosron and Li, 1986; Bosron et al., 1983), supporting *ADH1B*-rs1229984 as the possible causal variant.

A third limitation is that the cross-sectional nature of the sample might restrict our ability to determine the exact directionality of these associations. However, the direction modeled here is plausible. *ADH1B* is expressed once individuals begin drinking alcohol, so we only included those exposed to alcohol; thus, the *ADH1B* risk factor precedes both alcohol consumption and AUD development. Alcohol consumption must precede criterion endorsement and AUDs. To further address the temporality issue, a sensitivity analysis was conducted addressing AUD and criteria occurring within the 12 months before the interview (i.e., a current timeframe). The results were very similar to the analysis reported, further suggesting that the temporality of the model is plausible. In the future, these issues should be addressed using longitudinal data. Fourth, the lack of evidence for significant association between *ADH1B* and criteria with low prevalence (e.g., activities given up, neglect roles, and legal problems) may be attributable to low power, and the study should be repeated on a larger sample. However, this study remains informative about overall AUD and the criteria with higher prevalences. Last, because legal problems will be replaced by craving in DSM-5 (American Psychiatric Association, 2013), future studies should assess the relationship of *ADH1B* to alcohol craving, which was not available in this data set.

In conclusion, this study provides new information on the associations between *ADH1B* and AUDs and the DSM-IV AUD criteria (including effects through alcohol consumption), which enhances our understanding of the etiologic model through which AUDs can occur. For genetically complex disorders (e.g., AUDs), where numerous genes exert small effects on the broad clinical phenotype, identifying which aspects (i.e., criteria) are most informative in the association between *ADH1B* and AUDs advances our understanding of *ADH1B* effects.

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